

Exhibit B

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FINAL DOCUMENT

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Title: Essential Principles of Safety and Performance of Medical Devices

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This document was produced by the Global Harmonization Task Force, a voluntary international group of representatives from medical device regulatory authorities and trade associations from Europe, the United States of America (USA), Canada, Japan and Australia.

The document is intended to provide non-binding guidance to regulatory authorities for use in the regulation of medical devices, and has been subject to consultation throughout its development.

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Preface

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1 Introduction

The primary way in which the GHTF achieves its goals is through the production of a series of guidance documents that together describe a global regulatory model for medical devices. The purpose of such guidance is to harmonize the documentation and procedures that are used to assess whether a medical device conforms to the regulations that apply in each jurisdiction. Eliminating differences between jurisdictions decreases the cost of gaining regulatory compliance and allows patients earlier access to new technologies and treatments.

This document has been developed to encourage and support global convergence of regulatory systems. It is intended for use by Regulatory Authorities (RAs), Conformity Assessment Bodies (CABs) and industry, and will provide benefits in establishing, in a consistent way, an economic and effective approach to the control of medical devices in the interest of public health. It seeks to strike a balance between the responsibilities of RAs to safeguard the health of their citizens and their obligations to avoid placing unnecessary burdens upon the industry.

This guidance document describes fundamental design and manufacturing requirements, referred to as 'Essential Principles of Safety and Performance' that, when met, indicate a medical device is safe and performs to its specification. It **supersedes** an earlier version with the same title dated June 3rd, 2005 (GHTF/SG1/N041:2005). It has been changed to:

- respond to technical advancements since 2005 such as requirements for devices incorporating materials of biological origin, requirements for performance evaluation, and medical software; and
- provide a separate section within the document for IVD medical devices.

Where other guidance documents within the series are referenced within this text, their titles are italicised for clarity.

Study Group 1 of the Global Harmonization Task Force (GHTF) has prepared this guidance document. Comments or questions should be directed to the Chair of GHTF Study Group 1 whose contact details may be found on the GHTF web page¹.

2 Rationale, Purpose and Scope

2.1 Rationale

The worldwide adoption of fundamental design and manufacturing requirements for medical devices that, when met, provide assurance the device is safe and performs to its specification, offers significant benefits to the manufacturer, user, patient or consumer, and to Regulatory Authorities. Eliminating or reducing differences between jurisdictions decreases the cost of gaining regulatory compliance and allows patients earlier access to new technologies and treatments.

¹ www.ghtf.org

2.2 Purpose

To identify and describe six general essential principles of safety and performance that apply to all medical devices, including IVD medical devices.

To identify and describe additional essential principles of safety and performance which need to be considered during the design and manufacturing process, the first group of which is relevant to:

- medical devices **other than** IVD medical devices,

and the second group to

- IVD medical devices only.

Note: during the design process, the manufacturer² selects which of the listed design and manufacturing principles apply to the particular medical device and documents the reasons for excluding others.

2.3 Scope

This document applies to all products that fall within the definition of a medical device that appears within the GHTF document *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'*.

3 References

GHTF final documents³

GHTF/SG1/N78:2012 *Principles of Conformity Assessment for Medical Devices*.

GHTF/SG1/N70:2011 *Label and Instructions for Use for Medical Devices*.

GHTF/SG1/N044:2008 *Role of Standards in the Assessment of Medical Devices*.

GHTF/SG1/N055:2009 *Definitions of the Terms Manufacturer, Authorised Representative, Distributor and Importer*.

GHTF/SG1/N046:2008 *Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices*

GHTF/SG1/N071:2012 *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'*

GHTF/SG5/N1R8:2007 *Clinical Evidence – Key Definitions and Concepts*

GHTF/SG5/N2R8:2007 *Clinical Evaluation*.

² For the definition of manufacturer see GHTF/SG1/N055:2009 *Definitions of the Terms Manufacturer, Authorised Representative, Distributor and Importer*.

³ The listed documents are subject to periodic review and may be superseded by later documents. The reader is encouraged to refer to the GHTF website www.gh tf.org to confirm whether the referenced documents remain current.

GHTF/SG5/N3:2010 *Clinical Investigations*

GHTF/SG5/N6:2012 *Clinical Evidence for IVD Medical Devices - Key Definitions and Concepts*

GHTF/SG5/N7:2012 *Clinical Evidence for IVD Medical Devices - Scientific Validity Determination and Performance Evaluation.*

GHTF/SG5/N8:2012 *Clinical Performance Studies for In Vitro Diagnostic Medical Devices*

International standards

ISO 14971:2007 *Medical Devices – Application of Risk Management to Medical Devices.*

ISO/TR 16142:2006 *Medical Devices – Guidance on the Selection of Standards in Support of the Recognized Essential Principles of Safety and Performance of Medical Devices.*

4 Definitions

Analytical performance: the ability of an IVD medical device to detect or measure a particular analyte.

Clinical data: safety and/or performance information that are generated from the clinical use of a medical device.

Clinical evaluation: the assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer.

Clinical evidence for an IVD medical device: all the information that supports the scientific validity and performance for its use as intended by the manufacturer.

Clinical performance of an IVD medical device: the ability of an IVD medical device to yield results that are correlated with a particular clinical condition/physiological state in accordance with target population and intended user.

Harm: physical injury or damage to the health of people or damage to property or the environment

Hazard: potential source of harm.

Intended use / purpose: the objective intent of the manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the manufacturer

In Vitro Diagnostic (IVD) medical device: refer to GHTF/SG1/N71:2012 *Definition of the Terms ‘Medical Device’ and ‘In Vitro Diagnostic (IVD) Medical Device’.*

IVD medical device for self-testing: any IVD medical device intended by the manufacturer for use by lay persons.

Lay person: individual that does not have formal training in a relevant field or discipline.

Manufacturer: refer to GHF/SG1/N055:2009 Definitions of the Terms Manufacturer, Authorised Representative, Distributor and Importer.

Medical device: refer to GHF/SG1/N71:2012 *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'*.

Performance evaluation for an IVD medical device: assessment and analysis of data to establish or verify the performance of an IVD medical device.

Regulatory Authority (RA): a government agency or other entity that exercises a legal right to control the use or sale of medical devices within its jurisdiction, and may take enforcement action to ensure that medical products marketed within its jurisdiction comply with legal requirements.

Risk: combination of the probability of occurrence of harm and the severity of that harm.

Specimen: the discrete portion of a body fluid or tissue or other sample associated with the body taken for examination, study, or analysis of one or more quantity or characteristic to determine the character of the whole.

5 Safety and Performance of Medical Devices – General Principles

A manufacturer of a medical device is expected to design and manufacture a product that is safe and performs as intended. This guidance document describes fundamental design and manufacturing requirements, referred to as 'Essential Principles of Safety and Performance', to ensure this outcome. This document is structured to provide general essential principles that apply to all medical devices including IVD medical devices (Section 6) and is then separated into two dedicated sections, one for medical devices other than IVD medical devices (Section 7) and the other for IVD medical devices only (Section 8).

The medical device manufacturer's design and manufacturing activities are under the control of its quality management system. Conformity of the device to all the applicable Essential Principles will be demonstrated and assessed according to procedures designated by the Regulatory Authority and described in other GHF guidance.

6 Essential Principles applicable to all Medical Devices including IVD Medical Devices

- A1 Medical devices should be designed and manufactured in such a way that, when used under the conditions and for the purposes intended and, where applicable, by virtue of the technical knowledge, experience, education or training, and the medical and physical conditions of intended users, they will perform as intended by the manufacturer and not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.
- A2 The solutions adopted by the manufacturer for the design and manufacture of the devices should conform to safety principles, taking account of the generally

acknowledged state of the art. When risk reduction is required, the manufacturer should control the risks so that the residual risk associated with each hazard is judged acceptable. The manufacturer should apply the following principles in the priority order listed:

- identify known or foreseeable hazards and estimate the associated risks arising from the intended use and foreseeable misuse;
 - eliminate risks as far as reasonably practicable through inherently safe design and manufacture;
 - reduce as far as reasonably practicable the remaining risks by taking adequate protection measures, including alarms; and
 - inform users of any residual risks.
- A3 Medical devices should achieve the performance intended by the manufacturer and be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose.
- A4 The characteristics and performances referred to in Clauses A1, A2 and A3 should not be adversely affected to such a degree that the health or safety of the patient or the user and, where applicable, of other persons are compromised during the lifetime of the device, as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use and has been properly maintained in accordance with the manufacturer's instructions.
- A5 Medical devices should be designed, manufactured and packaged in such a way that their characteristics and performances during their intended use will not be adversely affected by transport and storage conditions (for example, fluctuations of temperature and humidity) taking account of the instructions and information provided by the manufacturer.
- A6 All known and foreseeable risks, and any undesirable effects, should be minimised and be acceptable when weighed against the benefits of the intended performance of medical devices during normal conditions of use.

7 Essential Principles applicable to Medical Devices other than IVD Medical Devices

The design and manufacturing principles listed in this Section of the document **are additional to the general principles of safety and performance listed in Section 6.**

B1 Chemical, physical and biological properties

- B1.1 The devices should be designed and manufactured in such a way as to ensure the characteristics and performance referred to in Section 6. Particular attention should be paid to:
- the choice of materials used, particularly as regards toxicity and, where appropriate, flammability,

- the compatibility between the materials used and biological tissues, cells, and body fluids taking account of the intended purpose of the device.
- the choice of materials used, reflecting, where appropriate, matters such as hardness, wear and fatigue strength.

B1.2 The devices should be designed, manufactured and packaged in such a way as to minimize the risk posed by contaminants and residues to the persons involved in the transport, storage and use of the devices and to patients, taking account of the intended purpose of the device. Particular attention should be paid to tissues exposed and to the duration and frequency of exposure.

B1.3 The devices should be designed and manufactured in such a way that they can be used safely with the materials, substances and gases with which they enter into contact during their normal use or during routine procedures; if the devices are intended to administer medicinal products they should be designed and manufactured in such a way as to be compatible with the medicinal products concerned according to the provisions and restrictions governing these products and that their performance is maintained in accordance with the intended use.

B1.4 The devices should be designed and manufactured in such a way as to reduce as far as reasonably practicable and appropriate the risks posed by substances that may leach or leak from the device. Special attention shall be given to substances which are carcinogenic, mutagenic or toxic to reproduction.

B1.5 Devices should be designed and manufactured in such a way as to reduce as far as reasonably practicable and appropriate risks posed by the unintentional ingress or egress of substances into or from the device taking into account the device and the nature of the environment in which it is intended to be used.

B2 Infection and microbial contamination

B2.1 The devices and manufacturing processes should be designed in such a way as to eliminate or to reduce as far as reasonably practicable and appropriate the risk of infection to patients, users and, where applicable, other persons. The design should:

- allow easy handling,

and, where necessary:

- reduce as far as reasonably practicable and appropriate any microbial leakage from the device and/or microbial exposure during use,
- prevent microbial contamination of the device or specimen, where applicable, by the patient, user or other person.

B2.2 Devices labelled as having a special microbiological state should be designed, manufactured and packaged to ensure they remain so when placed on the market and remain so under the transport and storage conditions specified by the manufacturer.

B2.3 Devices delivered in a sterile state should be designed, manufactured and packaged in a non-reusable pack, and/or according to appropriate procedures, to ensure that they

are sterile when placed on the market and remain sterile, under the transport and storage conditions indicated by the manufacturer, until the protective packaging is damaged or opened.

- B2.4 Devices labelled either as sterile or as having a special microbiological state should have been processed, manufactured and, if applicable, sterilized by appropriate, validated methods.
- B2.5 Devices intended to be sterilized should be manufactured in appropriately controlled (e.g. environmental) conditions.
- B2.6 Packaging systems for non-sterile devices should maintain the integrity and cleanliness of the product and, if the devices are to be sterilized prior to use, minimize the risk of microbial contamination; the packaging system should be suitable taking account of the method of sterilization indicated by the manufacturer.
- B2.7 The labelling of the device should distinguish between identical or similar products placed on the market in both sterile and non-sterile condition.

B3 Medical devices incorporating a substance considered to be a medicinal product/drug

This section is not intended to provide guidance on ‘combination products’ as a whole since definitions have yet to be harmonized and practice varies between different jurisdictions.

- B3.1 Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product/drug as defined in the relevant legislation that applies within that jurisdiction and which is liable to act upon the body with action ancillary to that of the device, the safety, quality and performance of the device as a whole should be verified, as well as the safety, quality and efficacy of the substance in the specific application,

B4 Medical devices incorporating materials of biological origin

This section is not intended to provide guidance on ‘combination products’ as a whole since definitions have yet to be harmonized and practice varies between different jurisdictions.

- B4.1 In some jurisdictions products incorporating tissues, cells and substances of animal origin may be considered medical devices. In this case, such tissues, cells and substances should originate from animals that have been subjected to veterinary controls and surveillance adapted to the intended use of the tissues. National regulations may require that the manufacturer and/or the Regulatory Authority retain information on the geographical origin of the animals. Processing, preservation, testing and handling of tissues, cells and substances of animal origin should be carried out so as to provide optimal safety for patients, users and, where applicable, other persons. In particular, safety with regard to viruses and other transmissible agents should be addressed by implementation of validated methods of elimination or inactivation in the course of the manufacturing process.
- B4.2 In some jurisdictions products incorporating human tissues, cells and substances may be considered medical devices. In this case, the selection of sources, donors and/or substances of human origin, the processing, preservation, testing and handling of tissues, cells and substances of such origin should be carried out so as to provide optimal safety for patients, users and, where applicable, other persons. In particular, safety with regard to viruses and other transmissible agents should be addressed by implementation of validated methods of elimination or inactivation in the course of the manufacturing process.
- B4.3 In some jurisdictions products incorporating cells and substances of microbial origin may be considered medical devices. In this case, processing, preservation, testing and handling of cells and substances should be carried out so as to provide optimal safety for patients, users and, where applicable, other persons. In particular, safety with regard to viruses and other transmissible agents should be addressed by implementation of validated methods of elimination or inactivation in the course of the manufacturing process.

B5 Environmental properties

- B5.1 If the device is intended for use in combination with other devices or equipment the whole combination, including the connection system should be safe and should not impair the specified performance of the devices. Any restrictions on use applying to such combinations should be indicated on the label and/or in the instructions for use. Connections which the user has to handle, such as fluid, gas transfer or mechanical coupling, should be designed and constructed in such a way as to minimize all possible risks from incorrect connection.
- B5.2 Devices should be designed and manufactured in such a way as to remove or reduce as far as reasonably practicable and appropriate:
- B5.2.1 the risk of injury to the patient, user or other persons in connection with their physical and ergonomic features;
 - B5.2.2 the risk of use error due to the ergonomic features, human factors and the environment in which the device is intended to be used;
 - B5.2.3 risks connected with reasonably foreseeable external influences or environmental conditions, such as magnetic fields, external electrical and electromagnetic effects, electrostatic discharge, radiation associated with

- diagnostic or therapeutic procedures, pressure, humidity, temperature or variations in pressure and acceleration;
- B5.2.4 the risks associated with the use of the device when it comes into contact with materials, liquids, and gases to which it is exposed during normal conditions of use;
- B5.2.5 the risk associated with the possible negative interaction between software and the environment within which it operates and interacts;
- B5.2.6 the risks of accidental penetration of substances into the device;
- B5.2.7 the risks of reciprocal interference with other devices normally used in the investigations or for the treatment given;
- B5.2.8 risks arising where maintenance or calibration are not possible (as with implants), from ageing of materials used or loss of accuracy of any measuring or control mechanism.
- B5.3 Devices should be designed and manufactured in such a way as to minimize the risks of fire or explosion during normal use and in single fault condition. Particular attention should be paid to devices whose intended use includes exposure to or use in association with flammable substances or substances which could cause combustion.
- B5.4 Devices should be designed and manufactured in such a way that adjustment, calibration, and maintenance, where such is necessary to achieve the performances intended, can be done safely.
- B5.5 Devices should be designed and manufactured in such a way as to facilitate the safe disposal of any waste substances.

B6 Devices with a diagnostic or measuring function

- B6.1 Diagnostic devices and devices with a measuring function, should be designed and manufactured in such a way as to provide sufficient accuracy, precision and stability for their intended purpose of the device, based on appropriate scientific and technical methods. The limits of accuracy should be indicated by the manufacturer.
- B6.2 Any measurement, monitoring or display scale should be designed in line with ergonomic principles, taking account of the intended purpose of the device.
- B6.3 Wherever possible values expressed numerically should be in commonly accepted, standardised units, and understood by the users of the device.

Note: While SG1 generally supports convergence on the global use of internationally standardised measurement units, considerations of safety, user familiarity, and established clinical practice may justify the use of other recognised measurement units.

B7 Protection against radiation

B7.1 General

- Devices should be designed and manufactured and packaged in such a way that exposure of patients, users and other persons to any emitted radiation should be reduced as far as reasonably practicable and appropriate, compatible with the intended purpose, whilst not restricting the application of appropriate specified levels for therapeutic and diagnostic purposes.

B7.2 Intended radiation

- Where devices are designed to emit hazardous, or potentially hazardous, levels of visible and/or invisible radiation necessary for a specific medical purpose the benefit of which is considered to outweigh the risks inherent in the emission, it should be possible for the user to control the emissions. Such devices should be designed and manufactured to ensure reproducibility of relevant variable parameters within an acceptable tolerance.
- Where devices are intended to emit potentially hazardous, visible and/or invisible radiation, they should be fitted, where reasonably practicable, with visual displays and/or audible warnings of such emissions.

B7.3 Unintended radiation

- Devices should be designed and manufactured in such a way that exposure of patients, users and other persons to the emission of unintended, stray or scattered radiation is reduced as far as reasonably practicable and appropriate.

B7.4 Ionizing radiation

- Devices intended to emit ionizing radiation should be designed and manufactured in such a way as to ensure that, where reasonably practicable, the quantity, geometry and energy distribution (or quality) of radiation emitted can be varied and controlled taking into account the intended use.
- Devices emitting ionizing radiation intended for diagnostic radiology should be designed and manufactured in such a way as to achieve appropriate image and/or output quality for the intended medical purpose whilst minimising radiation exposure of the patient and user.
- Devices emitting ionizing radiation, intended for therapeutic radiology should be designed and manufactured in such a way as to enable reliable monitoring and control of the delivered dose, the beam type and energy and where appropriate the energy distribution of the radiation beam.

B8 Medical devices that incorporate software and standalone medical device software

- ### **B8.1**
- Devices incorporating electronic programmable systems, including software, or standalone software that are devices in themselves, should be designed to ensure

repeatability, reliability and performance according to the intended use. In the event of a single fault condition, appropriate means should be adopted to eliminate or reduce as far as reasonably practicable and appropriate consequent risks.

- B8.2 For devices which incorporate software or for standalone software that are devices in themselves, the software must be validated according to the state of the art taking into account the principles of development lifecycle, risk management, verification and validation.

B9 Active medical devices and devices connected to them

- B9.1 For active medical devices, in the event of a single fault condition, appropriate means should be adopted to eliminate or reduce as far as reasonably practicable and appropriate consequent risks.
- B9.2 Devices where the safety of the patients depends on an internal power supply should be equipped with a means of determining the state of the power supply.
- B9.3 Devices where the safety of the patients depends on an external power supply should include an alarm system to signal any power failure.
- B9.4 Devices intended to monitor one or more clinical parameters of a patient should be equipped with appropriate alarm systems to alert the user of situations which could lead to death or severe deterioration of the patient's state of health
- B9.5 Devices should be designed and manufactured in such a way as to reduce as far as reasonably practicable and appropriate the risks of creating electromagnetic interference which could impair the operation of this or other devices or equipment in the usual environment.
- B9.6 Devices should be designed and manufactured in such a way as to provide an adequate level of intrinsic immunity to electromagnetic disturbance to enable them to operate as intended.
- B9.7 Devices should be designed and manufactured in such a way as to avoid, as far as reasonably practicable, the risk of accidental electric shocks to the patient, user or any other person, both during normal use of the device and in the event of a single fault condition in the device, provided the device is installed and maintained as indicated by the manufacturer.

B10 Protection against mechanical risks

- B10.1 Devices should be designed and manufactured in such a way as to protect the patient and user against mechanical risks connected with, for example, resistance to movement, instability and moving parts.
- B10.2 Devices should be designed and manufactured in such a way as to reduce to the lowest practicable level the risks arising from vibration generated by the devices, taking account of technical progress and of the means available for limiting vibrations, particularly at source, unless the vibrations are part of the specified performance.

- B10.3 Devices should be designed and manufactured in such a way as to reduce to the lowest practicable level the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source, unless the noise emitted is part of the specified performance.
- B10.4 Terminals and connectors to the electricity, gas or hydraulic and pneumatic energy supplies which the user has to handle should be designed and constructed in such a way as to minimize all possible risks.
- B10.5 Devices should be designed and manufactured in such a way as to reduce to the lowest practicable level, the risk of error when certain parts within the device are intended to be connected or reconnected before or during use.
- B10.6 Accessible parts of the devices (excluding the parts or areas intended to supply heat or reach given temperatures) and their surroundings should not attain potentially dangerous temperatures under normal conditions of use.
- B11 Protection against the risks posed to the patient or user by supplied energy or substances**
- B11.1 Devices for supplying the patient with energy or substances should be designed and constructed in such a way that the delivered amount can be set and maintained accurately enough to guarantee the safety of the patient and of the user.
- B11.2 Devices should be fitted with the means of preventing and/or indicating any inadequacies in the delivered amount which could pose a danger. Devices should incorporate suitable means to prevent, as far as possible, the accidental release of dangerous levels of energy or substances from an energy and/or substance source.
- B11.3 The function of the controls and indicators should be clearly specified on the devices. Where a device bears instructions required for its operation or indicates operating or adjustment parameters by means of a visual system, such information should be understandable to the user and, as appropriate, the patient.
- B12 Protection against the risks posed by medical devices intended by the manufacturer for use by lay persons**
- B12.1 Devices for use by lay persons should be designed and manufactured in such a way that they perform appropriately for their intended purpose taking into account the skills and the means available to lay persons and the influence resulting from variation that can reasonably be anticipated in the lay person's technique and environment. The information and instructions provided by the manufacturer should be easy for the lay person to understand and apply.
- B12.2 Devices for use by lay persons should be designed and manufactured in such a way as to reduce as far as reasonably practicable the risk of error during use by the lay person in the handling of the device and also in the interpretation of results.
- B12.3 Devices for use by lay persons should, where reasonably possible, include a procedure by which the lay person can verify that, at the time of use, the product will perform as intended by the manufacturer.

B13 Label and Instructions for Use

B13.1 Users should be provided with the information needed to identify the manufacturer, to use the device safely and to ensure the intended performance, taking account of their training and knowledge. This information should be easily understood ⁴.

B14 Clinical evaluation

B14.1 For all medical devices, the demonstration of conformity with essential principles includes a clinical evaluation in accordance with GHTF guidance. The clinical evaluation should review clinical data in the form of any:

- clinical investigation reports,
- literature reports/reviews, and
- clinical experience.

to establish that a favourable benefit-risk ratio exists for the device.

Note: Further information is provided in GHTF/SG5/N2R8:2007 *Clinical Evaluation*.

B14.2 Clinical investigations⁵ on human subjects should be carried out in accordance with the spirit of the Helsinki Declaration. This includes every step in the clinical investigation from first consideration of the need and justification of the study to publication of the results. In addition, some countries may have specific regulatory requirements for pre-study protocol review or informed consent.

8 Essential Principles applicable to IVD Medical Devices

The design and manufacturing principles listed in this Section of the document **are additional to the general principles of safety and performance listed in Section 6.**

⁴ Further information is provided in GHTF/SG1/N70:2011 *Label and Instructions for Use for Medical Devices*.

⁵ See GHTF/SG5/N3:2010 *Clinical Investigations*

C1 Chemical, physical and biological properties

- C1.1 The IVD medical devices should be designed and manufactured in such a way as to ensure the characteristics and performance referred to in Section 6. Particular attention should be paid to the possibility of impairment of analytical performance due to incompatibility between the materials used and the specimens and/or analyte (measurand) to be detected (such as biological tissues, cells, body fluids and micro-organisms), taking account of its intended purpose.
- C1.2 The IVD medical devices should be designed, manufactured and packaged in such a way as to minimize the risk posed by contaminants and residues to the persons involved in the transport, storage and use of the devices and to patients, taking account of the intended purpose of the device.
- C1.3 The IVD medical devices should be designed and manufactured in such a way as to reduce as far as reasonably practicable and appropriate the risks posed by substances that may leach or leak from the IVD medical device. Special attention should be given to substances which are carcinogenic, mutagenic or toxic to reproduction.
- C1.4 IVD medical devices should be designed and manufactured in such a way as to reduce as far as reasonably practicable and appropriate risks posed by the unintentional ingress or egress of substances into or from the IVD medical device taking into account the device and the nature of the environment in which it is intended to be used.

C2 Infection and microbial contamination

- C2.1 The IVD medical devices and manufacturing processes should be designed in such a way as to eliminate or to reduce as far as reasonably practicable and appropriate the risk of infection to user, professional or lay, or, where applicable, other person. The design should:
- allow easy and safe handling;
- and, where necessary:
- reduce as far as reasonably practicable and appropriate any microbial leakage from the IVD medical device and/or microbial exposure during use; and
 - prevent microbial contamination of the IVD medical device or specimen where applicable, by the user, professional or lay, or other person.

- C2.2 IVD medical devices labelled either as sterile or as having a special microbiological state should be designed, manufactured and packaged to ensure they remain so when placed on the market and remain so under the transport and storage conditions specified by the manufacturer, until the protective packaging is damaged or opened.
- C2.3 IVD medical devices labelled either as sterile or as having a special microbiological state should have been processed, manufactured and, if applicable, sterilized by appropriate, validated methods.
- C2.4 IVD medical devices intended to be sterilized should be manufactured in appropriately controlled (e.g. environmental) conditions.
- C2.5 Packaging systems for non-sterile IVD medical devices should maintain the integrity and cleanliness of the device.

C3 IVD medical devices incorporating materials of biological origin

- C3.1 Where IVD medical devices include tissues, cells and substances originating from animals, the processing, preservation, testing and handling of tissues, cells and substances of animal origin should be carried out so as to provide optimal safety for user, professional or lay, or other person.

In particular, safety with regard to viruses and other transmissible agents should be addressed by implementation of validated methods of elimination or inactivation in the course of the manufacturing process. This may not apply to certain IVD medical devices if the activity of the virus and other transmissible agent are integral to the intended purpose of the IVD medical device or when such elimination or inactivation process would compromise the performance of the IVD medical device.

National regulations may require that the manufacturer and/or the Regulatory Authority retain information on the geographical origin of the animals.

- C3.2 Where IVD medical devices include human tissues, cells and substances, the selection of sources, donors and/or substances of human origin, the processing, preservation, testing and handling of tissues, cells and substances of such origin should be carried out so as to provide optimal safety for user, professional or lay, or other person.

In particular, safety with regard to viruses and other transmissible agents should be addressed by implementation of validated methods of elimination or inactivation in the course of the manufacturing process. This may not apply to certain IVD medical devices if the activity of the virus and other transmissible agent are integral to the intended purpose of the IVD medical device or when such elimination or inactivation process would compromise the performance of the IVD medical device.

- C3.3 Where IVD medical devices include cells and substances of microbial origin, the processing, preservation, testing and handling of cells and substances should be carried out so as to provide optimal safety for user, professional or lay, or other person.

In particular, safety with regard to viruses and other transmissible agents should be addressed by implementation of validated methods of elimination or inactivation in the course of the manufacturing process. This may not apply to certain IVD medical

devices if the activity of the virus and other transmissible agent are integral to the intended purpose of the IVD medical device or when such elimination or inactivation process would compromise the performance of the IVD medical device.

C4 Environmental properties

- C4.1 If the IVD medical device is intended for use in combination with other devices or equipment, the whole combination, including the connection system should not impair the specified performance of the devices. Any restrictions on use applying to such combinations should be indicated on the label and/or in the instructions for use.
- C4.2 IVD medical devices should be designed and manufactured in such a way as to remove or reduce as far as reasonably practicable and appropriate:
- C4.2.1 the risk of injury to user, professional or lay, or other person in connection with their physical and ergonomic features;
 - C4.2.2 the risk of use error due to the ergonomic features, human factors and the environment in which the IVD medical device is intended to be used;
 - C4.2.3 risks connected with reasonably foreseeable external influences or environmental conditions, such as magnetic fields, external electrical and electromagnetic effects, electrostatic discharge, pressure, humidity, temperature or variations thereof;
 - C4.2.4 the risks associated with the use of the IVD medical device when it comes into contact with materials, liquids, and gases to which it is exposed during normal conditions of use;
 - C4.2.5 the risk associated with the possible negative interaction between software and the environment within which it operates and interacts;
 - C4.2.6 the risks of accidental penetration of substances into the IVD medical device;
 - C4.2.7 the risk of incorrect identification of specimens/samples;
 - C4.2.8 the risks of reasonably foreseeable interference with other devices such as carry over between IVD medical devices.

- C4.3 IVD medical devices should be designed and manufactured in such a way as to minimize the risks of fire or explosion during normal use and in single fault condition. Particular attention should be paid to IVD medical devices whose intended use includes exposure to or use in association with flammable substances or substances which could cause combustion.
- C4.4 IVD medical devices should be designed and manufactured in such a way that adjustment, calibration, and maintenance, where such is necessary to achieve the performances intended, can be done safely.
- C4.5 IVD medical devices should be designed and manufactured in such a way as to facilitate the safe disposal of any waste substances.

C5 Performance characteristics

- C5.1 IVD medical devices should be designed and manufactured in such a way that the performance characteristics support the intended use, based on appropriate scientific and technical methods. In particular, where appropriate, the design should address sensitivity, specificity, accuracy which is trueness and precision (repeatability and reproducibility), control of known relevant interference and limits of detection.

These performance characteristics need to be maintained during the lifetime of the IVD medical device as indicated by the manufacturer.

- C5.2 Where the performance of devices depends on the use of calibrators and/or control materials, the traceability of values assigned to such calibrators and/or control materials should be assured through available reference measurement procedures and/or available reference materials of a higher order.
- C5.3 Wherever possible values expressed numerically should be in commonly accepted, standardised units, and understood by the users of the device.

Note: While SG1 generally supports convergence on the global use of internationally standardised measurement units, considerations of safety, user familiarity, and established clinical practice may justify the use of other recognised measurement units.

C6 Protection against radiation

- C6.1 IVD medical devices should be designed, manufactured and packaged in such a way that exposure of user, professional or lay, or other person to the emitted radiation (intended, unintended, stray or scattered) is reduced as far as reasonably practicable and appropriate.
- C6.2 When IVD medical devices are intended to emit potentially hazardous, visible and/or invisible radiation, they should as far as reasonably practicable and appropriate be:
- designed and manufactured in such a way as to ensure that the characteristics and the quantity of radiation emitted can be controlled and/or adjusted; and
 - fitted with visual displays and/or audible warnings of such emissions.

C7 IVD medical devices that incorporate software and standalone IVD medical device software

- C7.1 For IVD medical devices which incorporate software or for standalone software that are IVD medical devices in themselves, the software must be validated according to the state of the art taking into account the principles of development lifecycle, risk management, verification and validation.

C8 IVD medical devices connected to, or equipped with, an energy source

- C8.1 IVD medical devices where the safety of the patient depends on an internal power supply in the IVD medical device, should be equipped with a means of determining the state of the power supply.
- C8.2 IVD medical devices should be designed and manufactured in such a way as to reduce as far as reasonably practicable and appropriate the risks of creating electromagnetic interference which could impair the operation of this or other devices or equipment in the usual environment.
- C8.3 IVD medical devices should be designed and manufactured in such a way as to provide an adequate level of intrinsic immunity to electromagnetic disturbance to enable them to operate as intended.
- C8.4 IVD medical devices should be designed and manufactured in such a way as to avoid, as far as reasonably practicable, the risk of accidental electric shocks to the user, professional or lay, or other person both during normal use of the device and in the event of a single fault condition in the device, provided the IVD medical device is installed and maintained as indicated by the manufacturer.

C9 Protection against mechanical and thermal risks

- C9.1 IVD medical devices should be designed and manufactured in such a way as to protect the user, professional or lay, or other person against mechanical risks connected with, for example, resistance to movement, instability and moving parts.
- C9.2 Where there are risks due to the presence of moving parts, risks due to break-up or detachment, or leakage of substances, then appropriate protection means must be incorporated.
- C9.3 IVD medical devices should be designed and manufactured in such a way as to reduce to the lowest practicable level the risks arising from vibration generated by the devices, taking account of technical progress and of the means available for limiting vibrations, particularly at source, unless the vibrations are part of the specified performance.
- C9.4 IVD medical devices should be designed and manufactured in such a way as to reduce to the lowest practicable level the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source.
- C9.5 Terminals and connectors to the electricity, gas or hydraulic and pneumatic energy supplies which the user, professional or lay, or other person has to handle should be designed and constructed in such a way as to minimize all possible risks.
- C9.6 IVD medical devices should be designed and manufactured in such a way as to reduce to the lowest practicable level, the risk of error when certain parts within the device are intended to be connected or reconnected before or during use.
- C9.7 Accessible parts of the IVD medical devices (excluding the parts or areas intended to supply heat or reach given temperatures) and their surroundings should not attain potentially dangerous temperatures under normal use.

C10 Protection against the risks posed by IVD medical devices for self-testing

- C10.1 IVD medical devices for self-testing should be designed and manufactured in such a way that they perform appropriately for their intended purpose taking into account the skills and the means available to lay persons and the influence resulting from variation that can reasonably be anticipated in the lay person's technique and environment. The information and instructions provided by the manufacturer should be easy for the lay person to understand and apply.
- C10.2 IVD medical devices for self-testing should be designed and manufactured in such a way as to reduce as far as reasonably practicable the risk of error by the lay person in the handling of the device and, if applicable, the specimen, and also in the interpretation of results.
- C10.3 IVD medical devices for self-testing should, where reasonably possible, include a procedure by which the lay person can verify that, at the time of use, the product will perform as intended by the manufacturer.

C11 Label and Instructions for Use

C11.1 Users should be provided with the information needed to identify the manufacturer, to use the device safely and to ensure the intended performance, taking account of their training and knowledge. This information should be easily understood⁶.

C12 Performance evaluation including analytical performance and, where appropriate, clinical performance

C12.1 For an IVD medical device a performance evaluation should be conducted in accordance with GHTF guidance. The performance evaluation should review analytical performance data and, where appropriate, clinical performance data in the form of any:

- literature;
- performance study reports; and
- experience gained by routine diagnostic testing.

to establish that the IVD medical device achieves its intended performance during normal conditions of use and that the known, and foreseeable risks, and any undesirable effects, are minimised and acceptable when weighed against the benefits of the intended performance.

C12.2 Clinical performance studies using specimens from human subjects should be carried out in accordance with the spirit of the Declaration of Helsinki. This includes every step in the clinical performance study from first consideration of the need and justification of the study to publication of the results. In addition, some countries may have specific regulatory requirements for informed consent.

⁶ Further information is provided in GHTF/SG1/N70:2011 *Label and Instructions for Use for Medical Devices*.